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EXAMINER

SPIEGLER, ALEXANDER H

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 01/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/936,299

Applicant(s)

HAGER, JOERG

Examiner

Alexander H. Spiegler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 23-53 is/are pending in the application.
- 4a) Of the above claim(s) 46-53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 23-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9/12/01. 6) ☐ Other: _____

DETAILED ACTION

Status of the Application

1. This action is in response to Applicant's election, filed on September 23, 2003.
Currently, Claims 23-53 are pending, Claims 23-45 are rejected herein, and Claims 46-53 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821. This action is made NON-FINAL.

Election/Restrictions

2. Applicant's election, with traverse, of Group I (Claims 23-45) is acknowledged.
However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

3. The information disclosure statement filed on September 12, 2001 complies with CFR 1.97, 1.98, and M.P.E.P. 609, and has been considered (see enclosed signed PTO-1449).

Priority

4. This application claims the benefit of PCT/EP00/02053, filed March 9, 2000, which claims priority to Federal Republic of Germany application 199 11 130.8, filed March 12, 1999.

Specification

5. The disclosure is objected to because of the following informalities:

A) The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

B) This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

C) The specification should be amended to include Applicant's claim of priority (see above section entitled, "Priority").

D) The use of the trademark "Quiaex II", "Z-Taq" has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

E) Claim 35 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, Claim 35 recites, "wherein said primer is complementary to *at least a part of said adaptor sequence.*" (emphasis added) Claim 23, from which Claim 35 depends from recites, "amplifying the adaptor-ligated restriction fragments...*using an adaptor-specific primer*" (emphasis added). In order for the amplification to occur the "adaptor-specific primer" must be complementary to at least a part of said adaptor sequence. Accordingly, because the "adaptor-specific primer" must be complementary to at least a part of said adaptor sequence, Claim 35 does not further limit Claim 23.

F) Claim 36 recites, “chosen from the group consisting of”, which could be amended to recite, “**selected** from the group consisting of”.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 23-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 23-45 are indefinite because Claim 23 is drawn to a method for the identification, isolation, or separation of identical nucleic acids fragments; however, the final step is for identifying, isolating, or separating the fully-matched heterohybrid fragments. The claims do not set forth the relationship between identical nucleic acids fragments and the fully-matched heterohybrid fragments. Therefore, it is not clear as to whether the claims are intended to be limited to a method of identification, isolation, or separation of identical nucleic acids fragments or the identification, isolation, or separation of the fully-matched heterohybrid fragments.

B) Claims 23-45 over “the fully-matched heterohybrid fragments” because this recitation lacks antecedent basis, since the recitation of “fully-matched heterohybrid fragments” does not appear prior to the recitation of “*the* fully-matched heterohybrid fragments”. Additionally, “the amplification products” and “the different nucleic acid populations” also lack antecedent basis. In Claim 23(c), the recitation of “the adaptor-ligated restriction fragment generated in step (a)”

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lacks antecedent basis because there is no adaptor ligated in step (a). Furthermore, Claims 37-45 are indefinite over “the homoduplexes”, “the heteroduplexes” and “the mismatched heterohybrid fragments” because these recitations lack antecedent basis. Finally, Claim 39 over “the hybridization mixture”, and Claim 40, step (b) over “the resulting mixture” for lack of antecedent basis. See MPEP 2173.05.

C) Claim 30 over “chromosome-specific and sequence-specific fashion” because it is not clear as to what steps encompass cloning in a “chromosome-specific and sequence-specific *fashion*”, and furthermore, this methodology is not defined in the specification. It is not clear whether this refers to the use of specific vectors or whether there is a specific process by which to clone in a “chromosome-specific and sequence-specific fashion”.

D) Claim 40, step (b) over “MutS-binding material” because it is not clear as to what material is considered to be “MutS-binding material”, this recitation is not an art-recognized term, and furthermore, this recitation is not defined in the specification.

E) Claim 42, step (e) because the claim contains information in parentheses, i.e. (blunt-ended). Parentheticals make the claims indefinite because it is unclear whether the information in the parentheses has the same, less, or more weight as the rest of the claim language. This rejection may be overcome by deleting the information the parentheses.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 23-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Weissman et al. (USPN 6,287,825).

Weissman teaches a method for the identification, isolation, or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations, comprising:

- (a) separately digesting the nucleic acids of said populations with at least one restriction enzyme (col. 4, lines 45-48, col. 7, lines 45-46, and cols. 11-14, for example);
- (b) ligating an adaptor sequence to the restriction fragments (col. 4, line 57 to col. 5, line 3, and col. 7, lines 50-53, and cols. 11-14, for example);
- (c) amplifying the adaptor-ligated restriction fragments generated in step (a) and in step (b) using an adaptor-specific primer (col. 2, 54-59, col. 4, line 57 to col. 5, line 3, and cols. 11-14, for example);
- (d) hybridizing the amplification products from the different nucleic acid populations with each other (col. 5, line 57 to col. 6, line 1, and cols. 11-14, for example); and
- (e) identifying, isolating, or separating the fully-matched heterohybrid fragments (col. 6, lines 2-8, col. 3, and cols. 11-14, for example).

Regarding Claims 24-25, Weissman teaches the nucleic acid populations comprise human genomic DNA populations (col. 4, lines 52-56, for example).

Regarding Claims 26-28, Weissman teaches the nucleic acid populations comprise nucleic acid populations from different subjects (or sources) having a common trait of interest

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and selected chromosomes (e.g., human chromosomes) (abstract and cols. 1, 3 and 4, for example).

Regarding Claim 29, Weissman teaches the restriction fragments are size-selected prior to amplification (cols. 4-5 and 7, for example). It is noted that Weissman's teaching of ligating adaptors only to restriction fragments can be interpreted as only amplifying "size-selected" fragments, as sequences that do not have adaptors are not selected for amplification.

Regarding Claim 30, Weissman teaches cloning a part of the restriction fragments (e.g., in a vector in a chromosome-specific and sequence specific fashion) (col. 6).

Regarding Claims 31-33, Weissman teaches the adaptors (Y-shaped, dsDNA adaptors comprising at least a 5 base long fragment) can contain restriction endonuclease sites for elimination of homohybrids or heterohybrids, such a recognition site can be GATC, which is specific for mutHL (cols. 1, 3, 7-8 and Figure 1(a), for example).

Regarding Claim 34, Weissman teaches the amplification can be via PCR (col. 2, lines 54-59, and col. 5, lines 4-22, for example).

Regarding Claim 35, Weissman teaches the primer is complementary to at least a part of the adaptor sequence (col. 5, lines 4-22 and cols. 7-8, for example).

Regarding Claim 36, Weissman teaches the primer can be labeled with a biotin tag at its 5' end (col. 3, lines 7-11, col. 5, lines 24-35, for example).

Regarding Claim 37, Weissman teaches separating heteroduplexes, identifying an eliminating mismatched heterohybrid and identifying, isolating or separating fully-matched heterohybrid fragments (cols. 1-3, for example).

Regarding Claims 38-39, Weissman teaches the eliminating step occurs via mismatch repair enzymes, such as MutH, MutS and MutL (cols. 1-2, for example).

Regarding Claim 40, Weissman teaches incubating the hybridization mixture with MutS and contacting the resulting product with a “MutS-binding material” (cols. 5-6 and 11-14, for example).

Regarding Claim 41 and 44-45, Weissman teaches separating heterohybrids from homohybrids based upon the labeling of the primer and methylation (cols. 1, 3 and 5, for example).

Regarding Claims 42-43, Weissman teaches digesting perfectly-matched DNAs by Exo III, and then single-stranded Exo III created strands by binding said single-stranded Exo III created strands using a strand specific matrix (col. 1, for example).

10. Claims 23-29 and 34-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Weissman et al. (USPN 6,150,112).

Weissman teaches a method for the identification, isolation, or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations, comprising:

- (a) separately digesting the nucleic acids of said populations with at least one restriction enzyme (col. 2, lines 46-48, col. 4, lines 30-34, and col. 6, lines 33-36, for example);
- (b) ligating an adaptor sequence to the restriction fragments (col. 4, line 40 to col. 5, line 5, and col. 6, lines 37-38, for example);
- (c) amplifying the adaptor-ligated restriction fragments generated in step (a) and in

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step (b) using an adaptor-specific primer (col. 4, line 40 to col. 5, line 5, and col. 6, lines 39-48, for example);

(d) hybridizing the amplification products from the different nucleic acid populations with each other (col. 5, lines 15-23, Figure 1(f), and col. 6, lines 57-65, for example); and

(e) identifying, isolating, or separating the fully-matched heterohybrid fragments (col. 5, lines 23-28, col. 6, lines 5-9 and line 55 to col. 7, line 18, for example).

Regarding Claims 24-25, Weissman teaches the nucleic acid populations comprise human genomic DNA populations (col. 2, lines 30-33, for example).

Regarding Claims 26-28, Weissman teaches the nucleic acid populations comprise nucleic acid populations from different subjects (or sources) having a common trait of interest and selected chromosomes (e.g., human chromosomes) (abstract, col. 1, col. 3, lines 32-36 and col. 4, lines 36-40, for example).

Regarding Claim 29, Weissman teaches the restriction fragments are size-selected prior to amplification (col. 2, lines 45-58, for example). It is noted that Weissman's teaching of ligating adaptors only to restriction fragments can be interpreted as only amplifying "size-selected" fragments, as sequences that do not have adaptors are not selected for amplification.

Regarding Claim 34, Weissman teaches the amplification can be via PCR (col. 4, lines 54-56, for example).

Regarding Claim 35, Weissman teaches the primer is complementary to at least a part of the adaptor sequence (col. 2, lines 50-55, for example).

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Regarding Claim 36, Weissman teaches the primer is labeled with a biotin tag at its 5' end (col. 2, lines 55-56, for example).

Regarding Claim 37, Weissman teaches separating heteroduplexes, identifying an eliminating mismatched heterohybrid and identifying, isolating or separating fully-matched heterohybrid fragments (cols. 1-2, for example).

Regarding Claims 38-39, Weissman teaches the eliminating step occurs via mismatch repair enzymes, such as MutH, MutS and MutL (cols. 1-2, for example).

Regarding Claim 40, Weissman teaches incubating the hybridization mixture with MutS and contacting the resulting product with a "MutS-binding material" (cols. 2 and 5, for example).

Regarding Claim 41 and 44-45, Weissman teaches separating heterohybrids from homohybrids based upon the labeling of the primer and methylation (cols. 1-2 and 4-5, for example).

Regarding Claims 42-43, Weissman teaches digesting perfectly-matched DNAs by Exo III, and then single-stranded Exo III created strands by binding said single-stranded Exo III created strands using a strand specific matrix (col. 1, for example).

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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12. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. Claims 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weissman et al. (USPN 6,150,112, herein referred to as '112), as applied to claims 23-29 and 34-45 above, and further in view of Weissman et al. (USPN 6,287,825, herein referred to as '825).

Weissman '112 teaches a method for the identification, isolation, or separation of identical nucleic acid fragments from a mixture of at least two nucleic acid populations comprising, digesting nucleic acids of said populations, ligating an adaptor to the digested fragments, amplifying the adaptor-ligated fragments, hybridizing the amplification products and identifying, isolating or separating fully matched heterohybrid fragments. Weissman '112 does not teach adaptors comprising recognition sites or cloning a part or all of the restriction fragments.

However, Weissman '825 teaches the adaptors (Y-shaped, dsDNA adaptors comprising at least a 5 base long fragment) can contain restriction endonuclease sites for elimination of homohybrids or heterohybrids, such a recognition site can be GATC, which is specific for mutHL (cols. 1, 3, 7-8 and Figure 1(a), for example). Specifically, Weissman teaches "restriction endonuclease recognition sites are present in the adapters such that homohybrid or heterohybrid DNA can be selectively eliminated" (col. 3, lines 45-48). Regarding Claim 30,

Weissman teaches cloning a part of the restriction fragments (e.g., in a vector in a chromosome-specific and sequence specific fashion) (col. 6).

Accordingly, in view of the teachings of Weissman '825, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Weissman '112 so as to have used adaptors comprising restriction endonuclease recognition sites. One of ordinary skill in the art would have been motivated to modify the method of Weissman '112, by using adaptors comprising restriction endonuclease recognition sites, in order to have achieved the benefit of selectively eliminating homohybrids or heterohybrids for effective identification, isolation or separation of DNA from two populations.

Furthermore, in view of the teachings of Weissman '825, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Weissman '112 so as to have cloned the restriction fragments (e.g., in a vector in a chromosome-specific and sequence specific fashion), in order to have achieved the benefit of enriching and selecting a desired gene sequences (responsible for a selected trait, for example).

Conclusion

14. No Claims are allowable.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Weissman et al. (USPN 6,372,434)

Grant et al. (USPN 6,524,794)

Firth et al. (USPN 6,573,053)

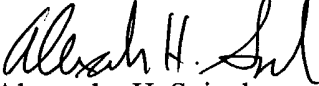
Brown et al. (USPN 5,376,526)

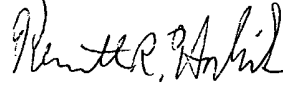
Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782. The fax number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.


Alexander H. Spiegler
January 22, 2004


KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
1/22/04